Research Article

The Correlation between Calcium Serum and Calcium Urine Level with the Blood Pressure in Preeclampsia

Hubungan antara Kadar Kalsium Darah dan Kadar Kalsium Urin dengan Tekanan Darah pada Preeklampsia

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Abstract

Objective: To analyze the differences of calcium serum and calcium urine level in preeclampsia and normal pregnancy, and to analyze the correlation between calcium serum and calcium urine level with blood pressure.

Method: This study is a cross sectional study with 44 women with preeclampsia and 45 women with normal pregnancies, that meet our inclusion criteria. The samples were obtained from Dr. Hasan Sadikin Hospital and six satellite hospitals from June to September 2011. The comparison of mean calcium serum and calcium urine level of the preeclampsia group was calculated using Mann-Whitney test, and the correlation between calcium serum and calcium urine level and preeclampsia were calculated using Rank Spearman correlation test.

Result: The result of the characteristic test in two groups of study shows that both groups are homogenic and comparable. The mean of calcium serum level in women with preeclampsia (7.97 mg/dl) is lower than in normal pregnancy (8.82 mg/dl) with p<0.0001 and the mean of calcium urine level in women with preeclampsia (1.725 mg/dl) is lower than normal pregnancy (2.809 mg/dl) with p<0.0001. There is a negative correlation between calcium serum level (rs = –0,62; p<0,001) and calcium urine level (rs = –0,68; p<0,001) with systolic pressure in preeclampsia. There is also a negative correlation between calcium serum level (rs = –0,65; p<0,001) and calcium urine level (rs = –0,68; p<0,001) with diastolic pressure in preeclampsia.

Conclusion: There is a negative correlation between calcium serum level and calcium urine level with systolic and diastolic pressure in preeclampsia, meaning that the lower the calcium serum and calcium urine level is, the higher systolic and diastolic pressure.

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Keywords: blood pressure, calcium blood level, calcium urine level, preeclampsia

Abstrak

***Tujuan**: Menganalisis perbedaan kadar kalsium darah dan kadar kalsium urin pada preeklampsia dan kehamilan normal dan menganalisis korelasi antara kadar kalsium darah dan kadar kalsium urin dengan tekanan darah pada preeklampsia.*

***Metode**: Rancangan penelitian ini adalah uji potong lintang (cross sectional) terhadap 44 subjek dengan preeklampsia dan 45 subjek dengan kehamilan normal yang memenuhi kriteria inklusi, yang datang ke RS Dr. Hasan Sadikin Bandung dan enam rumah sakit jejaring periode Juni – September 2011. Perbandingan rerata kadar kalsium darah dan kalsium urin preeklampsia dengan kehamilan normal dihitung menggunakan uji Mann-Whitney, dan korelasi antara kadar kalsium darah dan kadar kalsium urin dengan tekanan darah pada preeklampsia dihitung menggunakan uji korelasi Rank Spearman.*

***Hasil**: Uji karakteristik pada kedua kelompok penelitian menunjukkan kedua kelompok homogen dan dapat diperbandingkan. Rerata kadar kalsium darah pada preeklampsia lebih rendah (7,97 mg/dl) dibandingkan dengan kehamilan normal (8,82 mg/dl) dengan p<0,001. Rerata kadar kalsium urin pada preeklampsia lebih rendah (1,725 mg/dl) dibandingkan dengan kehamilan normal (2,809 mg/dl) dengan p<0,001). Terdapat korelasi negatif antara kadar kalsium darah (rs = – 0,62; (p<0,001) dan kadar kalsium urin (rs = – 0,68), (p<0,001) dengan tekanan darah sistolik pada preeklampsia. Terdapat korelasi negatif antara kadar kalsium darah (rs = – 0,65; (p < 0,001) dan kadar kalsium urin (rs = – 0,68; p < 0,001) dengan tekanan darah diastolik pada preeklampsia.*

***Kesimpulan**: Terdapat hubungan negatif antara kadar kalsium darah dan kadar kalsium urin dengan tekanan darah sistolik dan diastolik pada preeklampsia, yang berarti semakin rendah kadar kalsium darah dan kadar kalsium urin semakin tinggi tekanan darah sistolik dan diastolik.*

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***Kata kunci**: kalsium darah, kalsium urin, preeklampsia, tekanan darah*

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INTRODUCTION

Preeclampsia is a multi organ disorder in pregnancy, and until now the pathogenesis and etiology are still unknown. There have been many theories attempting to explain the pathogenesis and etiology, but there is no theory that could answer it for certain.

The incidence of preeclampsia in different countries varies between 2.6% - 7.3%, but worldwide, according to WHO is about 12%. The incidence of preeclampsia in Indonesia in 1980 - 2001 is between 6 to 8% of all pregnancies, with mortality rate ranging from 9.8 to 25%. In some hospitals in Indonesia, the incidence of preeclampsia is highly

variable. For example, in Dr. Cipto Mangunkusumo hospital, in 2002, the incidence is 9.17%, while based on annual reports from 2008 to 2009 Department of Obstetrics and Gynecology Faculty of Medicine University of Padjadjaran/Dr. Hasan Sadikin Hospital Bandung, the incidence of preeclampsia is about 11%.[1-5]

Preeclampsia does not show a rise in blood pressure until second trimester of pregnancy but the effect of vasoconstriction may occur earlier, and the change in vascular reactivity may be detected at 20 weeks of gestation. According to a survey, women who eventually developed preeclampsia had blood pressure slightly higher than normal threshold in second trimester of pregnancy.[6] Etiology and pathogenesis of preeclampsia are important to understood, so that the diagnosis of preeclampsia can be established as early as possible and therefore, clinicians can do a preventive management.[1,6] Preeclampsia preventions consist of interventions of the changes that occur in progression of disease, so that the complications are not even worse.[1,6]

Calcium is a mineral with the highest content in the human body. Nearly 99% of calcium in human body found in bone. The rest of it is found in blood plasma, in a bond with the protein and in ions form. Calcium plays important roles in various physiological functions of the human body, such as in the blood clotting process, maintaining cell membrane alongside sodium and potassium, as a signal transductor between hormone receptors, in neuromuscular activity, in enzymatic reactions, in the process of neurotransmission, maintaning the bone structure, and preservation of the calcium needed in the body.[7]

In pregnant woman, the need for calcium increases especially for bone formation of the fetus. In pregnant woman, normal level of total calcium in the blood increases in first trimester and then decline in the last trimester while blood calcium ion level increases. The highest level is reached in the last trimester. At birth, both total calcium level and blood calcium ion are lower.[8] Calcium is an important component in diet and the important regulator of cellular process including the vascular function. The change in calcium metabolism will cause a different calcium level in each component blood or urine.[8]

Calcium and preeclampsia are connected by calcium intake and metabolism of pregnant woman. Research about this correlation had been done and it proved that there was a correlation between calcium and preeclampsia.[9,10] Bellizan JM et al showed an increase in intracellular calcium level of smooth muscle of blood vessels will cause vasoconstriction easily that stimulate a rise of blood pressure.10 Yoshida et al revealed the different levels of hipocalciuri in preeclampsia and normal pregnancy, chronic hypertension, and gestational hypertension.[11] Irani YA showed that there was correlation between Angiotensinogene 1 type athletic-autoantibody ($AT_{1\text{-}AA}$) with preeclampsia and calcium. Another research showed that there was no correlation between calcium and preeclampsia.[12]

Until now, the mechanism and the correlation of calcium and preeclampsia are still unknown. [9,10]

METHOD

This study is a cross sectional study with 44 women with preeclampsia and 45 normal pregnancies, who meet the inclusion criteria. The samples were obtained from Dr. Hasan Sadikin Hospital Bandung and six-satellite hospitals from June to September 2011. The inclusion criterias in preeclampsia group include pregnant woman, viable fetus, > 28 weeks of gestation based on LMP and diagnosed as having preeclampsia, whilst the inclusion criteria in the control group are pregnant woman, viable fetus, >28 weeks of gestation based on LMP and diagnosed as a normal pregnancy. The exclusion criterias are pregnancy with complication, such as diabetes mellitus, renal disease, heart disease, pulmonary disease, chronic hypertension, and parturition.

The result of One Sample Kolmogorov Smirnov Test with Lilliefors Significance Correction test shows that the data is not distributed normally ($p \leq 0.05$). Therefore, the comparison of mean levels of blood and urinary calcium in pre-eclampsia with normal pregnancy are analyzed using the Mann-Whitney test, and the correlation between blood calcium and urinary calcium level with blood pressure in preeclampsia are analyzed using Rank Spearman correlation test.

RESULTS

Table 1 shows that there is no difference in subject characteristic according to age ($p=0.504$), parity ($p=0.0865$), and gestational age ($p=0.859$), thus these 2 groups are qualified for comparison.

Table 1. Characteristics of Research Subjects

Variable	Research Group				p*) Value
	Preeclampsia (n=44)		Normal Pregnancy (n=45)		
	n	%	n	%	
Age (year)					
≤ 20	8	18.2	6	13.3	0.504
21–34	24	54.5	30	66.7	
≥ 35	12	27.3	9	20.0	
Parity					
0–1	14	31.8	15	33.3	0.865
2–3	15	34.1	17	37.8	
≥ 4	15	34.1	13	28.9	
Gestational Age (Week)					
28–32	19	43.2	22	48.9	0.859
33–37	22	50.0	20	44.4	
38–42	3	6.8	3	6.7	

*Note: *)Chi Square test*

Table 2 shows that there is significant difference in blood calcium level (p<0.001) and in urinary calcium level (p<0.001) between preeclampsia and normal pregnancy.

Table 2. Comparison of Blood Levels of Calcium and Urine Calcium Levels in Preeclampsia and Normal Pregnancy

Variable	Research Group		p*) Value
	Preeclampsia (n=44)	Normal Pregnancy (n=45)	
Blood Calcium (mg/dl)			
Mean (SD)	7.970 (0.3670)	8.822(0.4497)	
Median	7.900	8.900	< 0.001
Range	6.9 – 8.8	7.5 – 9.5	
Urine Calcium (mg/dl)			
Mean (SD)	1.725 (0.4509)	2.809(0.3103)	
Median	1.800	2.800	< 0.001
Range	0.8 – 2.9	2.0 – 3.2	

*Note: *) Mann Whitney test*

Table 3 shows that there is a significant correlation between blood calcium levels with systolic blood pressure (p<0.001), with a negative correlation coefficient of 0.62 which indicates a very strong relationship between the decrease in blood calcium levels and increase in systolic blood pressure. There is also a significant relationship between urine calcium level with systolic blood pressure (p<0.001), with a negative correlation coefficient of 0.68, which indicates a very strong relationship between the decrease in urinary calcium levels and an increase in systolic blood pressure.

Table 3. Correlation between calcium serum level and calcium urine level with systolic pressure

Correlation with systolic blood pressure	Correlation coefficient (r)	p*) Value
Calcium blood level (mg/dl)	– 0.62	< 0.001
Calcium urine level (mg/dl)	– 0.68	< 0.001

*Note: *) Rank Spearman Correlation test*

Table 4 shows that there is a significant correlation between blood calcium level with diastolic blood pessure (p <0.001), with a negative correlation coefficient of 0.65, which indicates a very strong correlation between the decrease in blood calcium levels and the increase in diastolic blood pressure. There is also a significant correlation between urine calcium levels with diastolic blood pressure (p <0.001), with a negative correlation coefficient of 0.68 which indicates a very strong relationship between the decrease of urinary calcium levels and the increase of diastolic blood pressure.

Table 4. The relationship between blood calcium levels and urinary calcium levels with diastolic blood pressure

Correlation with diastolic blood pressure	Correlation coefficient (r)	p*) Value
Calcium blood level (mg/dl)	– 0.65	< 0.001
Calcium urine level (mg/dl)	– 0.68	< 0.001

*Note: *) Rank Spearman Correlation test*

DISCUSSION

Subjects Characteristics

Preeclampsia is a major cause of morbidity and mortality of mother and fetus. The incidence of preeclampsia for each country are different, since it is associated with many factors. According to WHO, several factors that influence the incidence of preeclampsia are parity, age, gestational age, ethnicity, socio-economic situation, etc. These characteristics serve as risk factors in the incidence of preeclampsia that have potential confounding variables that may affect the validity of the study.

The analysis showed that there is no significant difference between groups of preeclampsia and groups of normal pregnancy. In this study both treatment groups were homogeneous for age, parity, and gestational age, so they are comparable.

Comparison of Levels of Blood Calcium and Levels of Urine Calcium in Preeclampsia and Normal Pregnancy

McCarron revealed a decrease in blood calcium levels in hypertension when compared with normal pregnancies.[9] Bellizan and Punthumapol also reveals a decrease of blood calcium in patient with preeclampsia. State of low blood calcium is likely due to the lack of calcium intake or other pathophysiological processes in the body, resulting in an increase in parathyroid hormone (PTH). The increase of parathyroid hormone would lead to an increased intracellular calcium through a process of increasing cell membrane permeability to calcium and the activation and enhancement adenylcyclase cAMP (cyclic adenosine monophosphate), a consequence of mitochondrial calcium released into the cytosol. Intracellular calcium increasing in vascular smooth muscle would cause the blood vessels to be easily stimulated to vasoconstrict, which will eventually lead it to increase.[10,13]

Study by Yoshida et al revealed a decrease in urinary calcium in patient with preeclampsia.[11,14] In preeclampsia there is a change in almost all organ systems of the body, especially the cardiovascular, renal, hematologic and immunologic system. These changes are believed to be associated with an inadequate synthesis of vasoactive prostaglandin, which can cause uteroplacental circulation, kidney tissue and renal perfusion disturbance.[14,15] Hipocalciuria that occurs in preeclampsia is the expression of tubular dysfunction. Sanchez-Ramos et al studied the value of urinary calcium in 103 preeclamptic patients and found that in patient who later will develop preeclampsia, the excreted urinary calcium was significantly less than normal pregnancy.[16] Adjidé VS did a case-control studies of 47 preeclampsia patient and 50 control women and concluded that preeclampsia has hipocalciuria which is significantly lower than controls.[15] The occurrence of hipocalciuria in preeclampsia as sequences of events can be explained as follows: first, the decrease in vitamin D3 1.25 (dehydrocholesterol) or less calcium intake will reduce the absorption of calcium from the intestine, resulting in a decrease of ionized calcium in serum. Furthermore, it will cause an increase in parathyroid hormone and inhibition of transcription, which decreased it to an even lower level. Finally, parathyroid hormone causes increasing calcium reabsorption in the distal tubule, where hipocalciuria occured.[14,15]

In this study, there were differences in blood calcium levels and urinary calcium levels in preeclampsia compared to normal pregnancies. The blood calcium levels and urinary calcium level in preeclampsia is lower in normal pregnancies.

The Relationship between Blood Calcium Levels and Urinary Calcium Levels with Systolic Blood Pressure

Meta-analysis randomized control trial study from Bucher et al revealed a decrease in systolic blood pressure of –5.40 mmHg (95%CI, –7.81 for –3.00 mmHg; $p < 0.001$).[17] Irani RA describes the involvement of the renin-angiotensin system in preeclampsia, with the known role of angiotensin II type I ($AT_{1\text{-}AA}$) that involved in the pathophysiology of preeclampsia such as deposition of fibrin in endothelial cells and sub epithelium of renal that lead to the decrease of glomerular filtration rate (GFR), which causes kidney damage, and furthermore lead to disturbance of hemodynamic of the body system. The role of autoantibody angiotensin type 1 ($AT_{1\text{-}AA}$) is to increase calcium mobilization that stimulated from an increase in intracellular calcium in preeclampsia, resulting in an impaired calcium metabolism which cause a disruption of endothelial cells on the blood vessel, resulting in vasoconstriction of blood vessels.[12] Another mechanism of calcium and preeclampsia pathogenesis has been described by many other researcher.[9,10,13]

This study obtains a negative correlation between blood calcium levels and systolic blood pressure, which shows a strong correlation between the decrease of blood calcium levels and the increase of systolic blood pressure, which can be explained that the lower blood calcium levels, the higher systolic blood pressure could be reached. There is also a negative correlation between urinary calcium levels and systolic blood pressure, which shows a strong correlation between the decrease of urinary calcium levels and the increase of systolic blood pressure, which can be explained that the lower urinary calcium levels, the higher systolic blood levels could be reached.

The Relationship between Blood Calcium Levels and Urinary Calcium Levels with Diastolic Blood Pressure

Grobbee research revealed the correlation of calcium and blood pressure. It obtains the influence

of calcium on diastolic blood pressure, which is a decrease in diastolic blood pressure by 3.1 mmHg at 6th week and 2.4 mmHg.[18] The correlation and the influence of calcium on blood pressure can also be explained by Irani RA research, who revealed the role of $AT_{1\text{-}AA}$ in preeclampsia, which is causing a vasoconstriction of blood vessels.[12] Bucher et al also revealed a decrease in diastolic blood pressure of 0.24 mmHg.[17] The other researches explain another pathogenesis of calcium and preeclampsia.[9,10,13] Another mechanism of calcium and preeclampsia pathogenesis has been described.

This study obtains a negative correlation ($rs = -0.65$, $p < 0.001$) between blood calcium levels and diastolic blood pressure, which shows a strong correlation between the decrease in blood calcium levels and an increase in diastolic blood pressure, meaning that the lower blood calcium levels, the higher diastolic blood pressure could be reached. This study also found a negative correlation ($rs = -0.68$, $p < 0.001$) between urinary calcium levels and diastolic blood pressure, which shows a strong correlation between the decrease in urinary calcium levels and an increase in diastolic blood pressure, which can be explained that the lower urinary calcium levels, the higher diastolic blood pressure could be reached.

CONCLUSION

There is a negative correlation between calcium serum level and calcium urine level with systolic and diastolic blood pressure in preeclampsia, which means that the lower calcium serum and calcium urine level is, the higher systolic and diastolic pressure.

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